REMARKS

Claims, claim objection, and rejection of claims 1-2, 5, 12, and 17 under 35 USC § 112, second paragraph

Claims 1 and 5 were amended to recited an upper limit on the amount of p-hydroxybenzoate esters of 1 mg/ml. Support for these amendments is found on p. 4, ll. 25-30, of the application.

The claims were objected to and rejected as indefinite for the recitation of "p-hydroxybenzoate esters" in claim 5, the Office alleging that the recitation of this term in dependent claim 5 was seen as broadening the scope of the claim beyond that of independent claim 1 from which claim 5 depends. While the applicants respectfully traverse, in order to clarify claim 5 and expedite prosecution, claim 5 has been amended by inserting the definite article "the" before the recitation of "p-hydroxybenzoate esters." This amendment clarifies that the "p-hydroxybenzoate esters" referred to in claim 5 are the methyl parahydroxybenzoate and propyl parahydroxybenzoate recited in claim 1. It is respectfully submitted that this amendment merely clarifies claim 5 and does not narrow its scope.

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of claims 1-2, five, 12, and 17 under 35 USC 103

Claims 1-2, 5, 12, and 17 were rejected as obvious over DeLongueville et al. (WO 02/47689 A2) and Doron et al. The Office relied on DeLongueville for its teaching of cetirizine or an optical isomer (levocetirizine being identified as an optical isomer of cetirizine), liquid pharmaceutical compositions containing them, and a syrup containing cetirizine and methyl- and propylparaben. The Office notes that DeLongueville does not specifically teach an embodiment comprising levocetirizine and a mixture of methyl- and propylparaben nor the total amount of parabens or their ratios. The office relies on Doron for its teachings of the antibacterial effects of methylparaben (MP) and propylparaben (PP) with concentration ratios of [MP]:[PP] up to 8.33:1 and the synergistic antibacterial effects of combinations of parabens. For the following reasons, the applicants respectfully traverse.

The presently amended claims recite liquid levocetirizine compositions comprising [MP]:[PP] = 9:1 with a total urban concentration of [MP] + [PP] < 1 mg/ml. The lowest total

concentration of the combination of MP and PP taught by Doron to be completely antibacterial is 1.55 mg/ml. The applicants respectfully submit that it would have been nonobvious to reduce the concentrations of parabens to less than 1.55 mg/ml, let alone by more than 35%, down to 1 mg/ml. This is because those of ordinary skill in the art understand that for pharmaceutical compositions there can be zero tolerance for bacterial growth. There must be 100% certainty that each and every dosage form will be completely bacteria-free. But, following the teachings of Doron, one of ordinary skill in the art would avoid using smaller concentrations (i.e., below 1.5 mg/ml) because they would believe or reasonably expect that concentrations such as those recited in the present claims would render a composition susceptible to bacterial growth. While, as the Office noted, Doron teaches that combinations of parabens have a synergistic effect on planktonic bacteria, in the very same sentence Doron states, "although a complete antibacterial effect is not always achieved." The significance of this statement cannot be over-emphasized because to be safe, useful, and achieve regulatory approval, a complete antibacterial effect must be achieved. Furthermore, the antibacterial efficacy of a pharmaceutical composition must be continuously maintained over long periods of time and multiple potential exposures to bacteria. While liquid pharmaceutical formulations are manufactured to be bacteria-free and sealed, they may be repeatedly exposed to the risk of bacterial contamination each time the container is opened (such as with drops). And acceptable pharmaceutical formulation must be completely bacterial resistant under such circumstances throughout the life of the product.

Doron reports that solutions with [MP] + [PP] < 1.55 mg/ml (all of which, by the way, have a [MP]:[PP] ≤ 2) show planktonic bacterial growth. While the same combinations of parabens have complete antibacterial effect at 0.9 mg/ml on immobilized bacteria, Doron expressly states that there is a stronger antibacterial effect on immobilized bacteria compared to planktonic bacteria. So, one of ordinary skill in the art would understand from Doron that higher concentrations of parabens are required for liquid compositions.

In summary, the applicants respectfully submit that one of ordinary skill in the art could not have predicted or had a reasonable expectation that a liquid levocetirizine-containing solution would be completely antibacterial with concentrations of the combination of methyl- and propylparabens of less than 1 mg/ml because,

1. The lowest completely antibacterial concentration of the combination of MP + PP disclosed by Doron is > 1.5 mg/ml, the lower concentrations tested being reported to have bacterial growth;
2. Doron teaches that a complete antibacterial effect of a combination of parabens is not always achieved; and
3. Doron teaches that antibacterial efficacy of parabens is weaker against planktonic bacteria compared to immobilized bacteria.

It is therefore unexpected and nonobvious that compositions according to the claims would have such antibacterial efficacy. The unexpected efficacy of the claimed compositions is manifested in Tables 15-20 of Example 4 of the present application, which show that levocetirizine compositions according to claim 1 with total paraben concentrations ([MP] + [PP]) of from 0.375 mg/ml up to 1.125 mg/ml (and [MP]:[PP] = 9) are free of *Pseudomonas aeruginosa*, *E. coli,* and *Staphylococcus aureus* bacteria 14 and 28 days following inoculation with these bacteria, respectively.[1]

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

Date: April 24, 2009

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[1] *Candida albicans* and *Aspergillus niger* are fungi.